REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested.

As correctly stated in the Official Action and the Advisory Action, claims 10, 12-22, 24, 25, and 27-29 are pending in the present application. Claims 10, 12-22, 24, 25, and 27-29 stand rejected.

By the present amendment, independent claims 10, 28, and 29 have been amended to recite "treating the destruction of functional tissue." Support for this amendment can be found, at least, on page 5, lines 14 to the end of page 6. Claim 10 has been further amended to delete "chronic bronchitis." Claims 18-22 have been amended to depend from claim 28, rather than claim 17, which has been canceled. New dependent claims 30-40 have been added. Support for these claims can be found, at least, on pages 12-15 of the present specification. No new matter has been added. Applicants expressly reserve the right to file a continuation/divisional application on any subject matter canceled by the present amendment.

Interview Summary

Applicants gratefully acknowledge the courtesy shown by Examiner Owens to Applicants' undersigned representative in a personal interview on April 18, 2003.

During the interview the rejections under 35 U.S.C. §§ 112 and 103 were discussed. In particular, the Examiner suggested replacing the recitation of "prevention" with "treating" to overcome the rejection under 35 U.S.C. § 112, first paragraph.

Additionally, Applicant's representative discussed deleting the recitation of "chronic bronchitis" from claim 10. Applicants' representative further pointed out that the severity of the diseases recited in claim 10 would not lead one skilled in the art to believe that they could be treated with a compound only known to inhibit 5- lipoxygenase.

Request for Interview

In light of the length of pendency of the above-identified application, Applicants respectfully request an interview with the Examiner and the Examiner's supervisor. However, should the amendments and arguments contained in this Reply & Amendment put the application in consideration for allowance, such an interview is, of course, unnecessary. A separate Request for Interview is submitted herewith.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 10, 17, 28, and 29 (and claims depending therefrom) stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Claim 17 has been canceled, thereby mooting this rejection as it applies to this claim. Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, independent claims 10, 28, and 29 have been amended to recite "treating the destruction of functional tissue," rather than "preventing," as suggested by the Examiner in the interview of April 18, 2003.

The Advisory Action mailed June 11, 2003, indicates that such an amendment would invoke a 35 U.S.C. § 112, first paragraph, rejection, "given that the state of the art

teaches that 'the mere fact that a compound inactivates HLE in vitro is not in itself a guarantee for a physiological role.'" (citing the Bernstein reference). This rejection, to the extent, that it may apply to the claims as amended, is respectfully traversed.

Applicants respectfully submit that this is not the standard for enablement. Enablement does not require a an absolute **guarantee** that an particular invention will work *in vivo*, if it is shown to work *in vitro*. The standard for enablement for chemical/pharmaceutical inventions is discussed in *M.P.E.P.* §2164.02:

> If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against the correlation and decide whether one skilled in the art would accept the model as reasonably correlated to the condition. *In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Withdrawal of this rejection is respectfully requested.... A rigorous or invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985): [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

M.P.E.P. §2164.02.

Thus, a simple statement in the Bernstein reference that *in vitro* activity does not always produce corresponding *in vivo* activity does not nullify the enablement of the presently claimed invention. In fact, Bernstein et al. still accept the general proposition that a compound that inhibits HLE *in vitro* may elicit *in vivo* inhibition. Bernstein et al. further cite the Bieth reference on page 65 as helping to further predict which compounds are likely to elicit *in vivo* inhibition based on standard enzyme kinetics. Accordingly, the

skilled artisan does accept that *in vitro* inhibition of HLE corresponds to *in vivo* inhibition. The fact that **any** compound or composition **may** be inactivated, excreted, etc. before causing its intended effect does not render the use of the claimed compound or composition not enabled. The courts have never required an exhaustive study of *in vivo* pharmacokinetics/pharmacodynamics for a finding of enablement. This would appear to be especially true when techniques to determine such effects are well known in the art, as in the present case. The statement by Bernstein et al. is nothing more than a standard disclaimer stating that some compounds may have a slow enough rate of inhibition that they are inactivated before they can take effect. Bernstein et al. **do not** state that many or most *in vitro* HLE inhibitors are likely to be ineffective *in vivo*. Interestingly, Bernstein et al. point out (on page 65) that even slow inhibitors of HLE have been shown to be efficacious.

Bernstein et al. and the present specification both describe the well-known destructive nature of HLE on tissue. The present specification demonstrates that boswellic acid derivatives are capable of inhibiting HLE *in vitro*. Accordingly, in light of the current case law, Applicants respectfully submit that such evidence is sufficient to support enablement for the use of these compounds *in vivo* to treat the destruction of functional tissue as in the presently claimed invention. Contrary to the Examiner's statement in the Advisory Action, a 35 U.S.C. § 112, first paragraph, rejection is **not** warranted. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 10, 12-22, 24, 25, and 27 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Ammon et al. (EP 0 552 657) in view of Mulshine et al. (WO 95/24894) and Han (*Chin. Med. Sci. J.* 9(1):61-69). The Examiner argues that Ammon et al. recognizes that boswellic acid can be used for prophylaxis or control of inflammatory processes caused by elevated leukotriene formation. The Examiner asserts that Ammon et al. disclose the use of boswellic acid for treatment of inflammatory conditions of the joints, bronchitis, chronic hepatitis, and chronic asthma. The Examiner concludes that Ammon et al. recognize the use of boswellic acid to treat the same conditions as the presently claimed invention. Claim 17 has been canceled, thereby mooting this rejection as it applies to this claim. Claims 18-21 have been amended to depend from claim 28, which is not included in this rejection. Accordingly, the Mulshine et al. and Han publications are not discussed further here. This rejection, as it applies to independent claim 10, as amended, and claims 12-16 and 24-27, is respectfully traversed.

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that the cited publications do not disclose or suggest all of the claim limitations nor provide a reasonable expectation of success.

The present invention is drawn to methods of combating **severe** diseases, such as pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis, glomerulonephritis, and rheumatoid arthritis. The diseases to be treated by the present

invention are characterized by damage to functional tissue caused by release of leucocytic elastase. The methods of the present invention comprise administering an effective amount of boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof.

As noted in the specification, the inhibition of leucocytic elastase is important because, during the pathophysiological processes of the diseases being treated, this enzyme (which is released from activated neutrophilic granulocytes) plays an important part in the destruction of functional tissue. Thus, the aim of the present invention is to block the final destruction of tissues and organs resulting from the indicated diseases. Until Applicants discovered that boswellic acid inhibits leucocytic elastase, it was not known that boswellic acid could be used for such a purpose.

In the prior art, 5-lipoxygenase inhibitors, such as boswellic acids, had only been claimed to be useful for treating mild to moderate diseases, such as asthma. There was no indication in the prior art that 5-lipoxygenase inhibitors could be used to treat more severe diseases, such as those treated by the present invention. Thus, there was no reasonable expectation of success.

Ammon et al. disclose the use of boswellic acid compounds for treating inflammation in some diseases by inhibiting leukotriene synthesis. Although Ammon et al. lists among the diseases to be treated "diseases of the joints (rheumatism)," Applicants note that rheumatoid arthritis (which is treated by the present invention) is very different from other rheumatoid diseases. Rheumatoid arthritis is based on the destruction of the articular cartilage, in contrast to other rheumatoid diseases. This destruction leads to an irreversible

deformation of the joint which hinders movement. The destruction of the articular cartilage is **not prevented** by other drugs for the treatment of rheumatoid arthritis, such as inhibitors of cyclooxygenase or 5-lipoxygenase. Thus, rheumatoid arthritis is a very different disease than rheumatism, and **cannot be treated** by similar drugs. Applicants further note that claim 10, as amended, does not recite any of the same diseases discussed in the Ammon et al. publication, but rather recites more serious diseases that can be treated by inhibiting human leucocytic elastase. Thus, Ammon et al. do not disclose or suggest all of the limitations of the presently claimed invention.

Thus, although Ammon et al. may disclose the use of boswellic acid for influencing inflammation, such a disclosure would not suggest the present invention, which uses boswellic acid for combating more serious diseases and conditions caused by an increase in leucocytic elastase activity. In the Advisory Action, the Examiner states that because [t]he base/target of the diseases treated that applicant claims is inflammation, therefore, regardless of the severity of these diseases, one of skill in the art would still be motivated to use boswellic acid for the treatment of the inflammation based diseases per the teachings of Ammon and Mulshine." Applicants respectfully submit that this statement is incorrect. While there could be an inflammatory component to some of the diseases recited in the present claims (pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis (mucoviscidosis), glomerulonephritis, and rheumatoid arthritis) caused by the destruction of functional tissue that occurs, this does not mean that one skilled in the art would treat these diseases with anti-inflammatory compounds, particularly boswellic acid. The Examiner's statement is akin to implying that one can effectively treat cystic fibrosis

with aspirin, another anti-inflammatory compound. Such a treatment regimen would not be efficacious. Similarly, because boswellic acid was known to inhibit 5-lipoxygenase, this would not lead one skilled in the art to believe that this compound can be used to treat severe diseases such as that claimed. Accordingly, there is no reasonable expectation of success in treating the severe diseases claimed with a simple anti-inflammatory compound, much less boswellic acid. If the Examiner maintains this position, Applicants respectfully request that the Examiner provide documentary evidence or an Examiner's affidavit to this effect, rather than a broad conclusory statement.

Applicants respectfully submit that because **some** pentacyclic triterpenes were known to inhibit HLE, this is not sufficient to lead the skilled artisan to believe that all pentacyclic triterpenes do so. The Ying et al. publication cited in the specification on page 3 only tested several pentacyclic triterpenes, which were found to have a range of activity toward this enzyme; *i.e.*, some possessed poor Ki values. Applicants previously submitted, as Exhibit A ,with the response filed April 29, 2003, a review article (J. Patocka, *J. Appl. Biomed.* 1:7-12 (2003)). This article notes that there are **at least 4000** known triterpenes, with a wide spectrum of biological activities. *See* abstract. Thus, one skilled in the art would not reasonably conclude that boswellic acid would inhibit HLE, nor would be motivated to select boswellic acid out of the numerous pentacyclic triterpenes known.

In summary, Ammon et al. do not disclose or suggest that the severe diseases recited in the presently claimed invention can be treated with boswellic acid. Moreover, neither Ammon et al. nor any other publication disclose or suggest that boswellic acid

could be used to inhibit human leucocytic elastase. It was not until the present inventors discovered that boswellic acid could inhibit HLE that the presently claimed invention was possible. Accordingly, the cited publications do not disclose or suggest all of the claimed limitations. Withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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Date: June 25, 2003

Attachment to REPLY & AMENDMENT dated June 25, 2003

Marked-up Claims 10, 18-22, 28, and 29

10. (Five Times Amended) A method for combating diseases selected from the group consisting of pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis (mucoviscidosis), [chronic bronchitis,] glomerulonephritis and rheumatoid arthritis, which are caused by increased leucocytic elastase or plasmin activity or can be treated by the inhibition of normal leucocytic elastase or plasmin activity, said method comprising administering boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof, in an amount effective for [preventing] treating the destruction of functional tissue, to combat said diseases to a mammalian organism in need of such combating.

18. (Amended) The method as claimed in claim [17] 28, wherein said boswellic acid is administered intraperitoneally, orally, buccally, rectally, intramuscularly, topically, subcutaneously, intraarticularly, intravenously or inhalationally.

19. (Amended) The method as claimed in claim [17] 28, wherein said boswellic acid is administered in the form of tablets, dragees, capsules, solutions, emulsions, ointments, creams, inhalants, aerosols or suppositories.

Attachment to REPLY & AMENDMENT dated June 25, 2003

Marked-up Claims 10, 18-22, 28, and 29

20. (Amended) The method as claimed in claim [17] 28, wherein said mammalian organism is an animal.

21. (Amended) The method as claimed in claim [17] 28, wherein said mammalian organism is a human.

22. (Amended) The method as claimed in claim [17] 28, wherein a pharmaceutical compound is also present.

28. (Amended) A method for [preventing] treating the destruction of functional tissue associated with diseases selected from the group consisting of pulmonary emphysema, acute respiratory distress syndrome, shock lung, cystic fibrosis (mucoviscidosis), chronic bronchitis, glomerulonephritis and rheumatoid arthritis, which are caused by increased leucocytic elastase or plasmin activity or can be treated by the inhibition of normal leucocytic elastase or plasmin activity, said method comprising administering boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof, in an amount effective for [preventing] treating the destruction of functional tissue, to a mammalian organism in need of such [prevention] treatment.

Attachment to REPLY & AMENDMENT dated June 25, 2003

Marked-up Claims 10, 18-22, 28, and 29

29. (Amended) A method for [preventing] treating the destruction of functional tissue associated with tumors and neoplasms or tumor metastases which are caused by increased plasmin activity or can be treated by the inhibition of normal leucocytic elastase or plasmin activity, said method comprising administering boswellic acid, a physiologically acceptable salt, a derivative, a salt of the derivative, a plant extract containing boswellic acid, or combinations thereof, in an amount effective for [preventing] treating the destruction of functional tissue, to a mammalian organism in need of such [prevention] treatment.

APPLICANT INITIATED INTERVIEW REQUEST FORM

Application No.:	09/011,977	First Named Applicant:	Hermann P.T. AMMON
Attorney's Dkt. No.:	015200-054	Examiner:	Howard V. Owens
Group Art Unit:	1623	Status of Application:	

Tentative Participants: (1) Jennifer Topmiller (2) Mary Katherine Baumeister (3) Examiner H. Owens (4) Examiner J. Wilson

Proposed Date of Interview: as soon as convenient Proposed Time: Flexible ____ AM ____ PM

Type of Interview Requested: (1) Telephonic (2) X Personal (3) Video Conference

Exhibit To Be Shown Or Demonstrated: Yes X No

If yes, provide brief description:

ISSUES TO BE DISCUSSED

Issues (Rej., Obj., etc.)	Claims/ Fig. #s	Cited Documents	Discussed	Agreed	Not Agreed
(1) § 112 rejection	All		[ ]	[ ]	[ ]
(2) § 103 rejection	mainly claim 10	Ammon et al.	[ ]	[ ]	[ ]
(3)			[ ]	[ ]	[ ]
(4)			[ ]	[ ]	[ ]

[ ] Continuation Sheet Attached

Brief Description of Arguments to be Presented:

See attached Reply & Amendment Pursuant to 37 C.F.R. § 1.114 and possible declaration re § 103 rejections.

An interview was conducted on the above-identified application on _____.

NOTE: This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01). This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 C.F.R. § 1.133(b)) as soon as possible.

_____ _____

Applicant's / Applicants' Representative Signature
Reg. No. 50,435

Examiner / SPE Signature

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